REMARKS

Claims 61, 62, 66, 68, 76 and 77 have been amended to recite biological functions of CRSP-2 protein. Support for the amendments is found, for example, at page 11, line 22 *et seq.*

Rejection of Claims 61-88 Under 35 U.S.C. §§ 101 and 112, First Paragraph

Claims 61-88 are rejected under 35 U.S.C. § 101 as not being supported by a specific, substantial or well established utility, and under 35 U.S.C. § 112, first paragraph, as not being enabled.

Applicant maintains that the rejected claims satisfy the utility requirement of 35 U.S.C. § 101 and the enablement requirement of 35 U.S.C. § 112 for the reasons presented in the Amendment filed on May 12, 2004, which are incorporated herein by reference. Specifically, the Examiner appears to be looking for an assertion of utility that has a degree of particularity that amounts to disclosure of how or why the invention works, *e.g.*, the molecular interactions or molecular mechanisms underlying the utility of CRSP-2. This approach is inconsistent with the case law and with the PTO Utility Examination Guidelines ("Guidelines," MPEP § 2107, 8th ed., Rev.1 (Feb. 2003)). It is well-established that "it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." In re Cortright, 165 F.3d 1353, 1359, 49 USPQ2d 1464, 1469 (Fed. Cir. 1999) (quoting Newman v. Quigg, 877 F.2d 1575, 1581, 11 USPQ2d 1340, 1345 (Fed. Cir. 1989)). "Furthermore, statements that a physiological phenomenon was observed are not inherently suspect simply because the underlying basis for the observation cannot be predicted or explained." Id.

The Examiner states that he is not requiring Applicant to disclose how the invention works. However, this statement appears to be belied by the Examiner's additional remarks. For example, the Examiner repeatedly states that there is no disclosure of "specific biological properties" of CRSP-2. (Office Action at page 3 and 4.) The Examiner also comments on the disclosures of Krupnick *et al.* (Reference DQ of record) and Mao *et al.* (Reference AS of record), which provide evidence that CRSP-2 (Dkk4) inhibits signal transduction as Applicant discloses, stating that these references only disclose that CRSP-2 "cooperates with Krm2 in some

undisclosed manner to inhibit Wnt signalling," and that additional research was required to ascertain "even this limited concept of what biological functions CRSP-2 actually performs." (Office Action at pages 4 and 5.) These additional remarks demonstrate that the Examiner considers disclosure of an explanation of how or why CRSP-2 has an asserted utility (*e.g.*, modulation of cellular signal transduction, regulation of gene transcription and/or regulation of cellular proliferation) to be required to meet the utility requirement. This is legally improper.

The Court of Appeals for the Federal Circuit addressed the requirements of 35 U.S.C. § 112, and the underlying utility requirement of 35 U.S.C. § 101, in the context of claims drawn to novel compounds in In re Brana, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). (The Brana court also restated the well-known rule of law that human testing is not a prerequisite to patentability of compounds with asserted therapeutic utility.)

The application in Brana claimed 5-nitrobenzo[de]isoquinoline-1,3-dione compounds and taught that the compounds were "antitumor substances." Id. at 1562, 34 USPQ2d at 1437-38. The Examiner rejected the claims under 35 U.S.C. § 112, first paragraph, based specifically on a challenge to the utility of the claimed compounds and the amount of experimentation needed to use the compounds. Id. During prosecution, the applicants provided test results that showed that several of the compounds had antitumor activity in a standard tumor model. Id. at 1567, 34 USPQ2d at 1441. Despite the evidence showing utility of the compounds, the Board affirmed the rejection based specifically on a challenge to the utility of the claimed compounds and the amount of experimentation needed to use the compounds. Id. at 1562, 34 USPQ2d at 1437-38.

On appeal, the decision of the Board was reversed. Id. at 1562, 34 USPQ2d at 1437. The court explained that the Patent Office has the initial burden of challenging a presumptively correct assertion of utility in the specification. Id. at 1556, 34 USPQ2d at 1441. The court found that in view of the numerous examples of chemotherapeutic agents known in the art at that time, the person of skill in the art would be without basis to reasonably doubt the applicants' assertion that the claimed compounds were "antitumor substances." Id. Accordingly, the court held that the applicants should not have been required to substantiate their asserted utility to avoid rejection. Id. In addition, the court further stated that even if the Patent Office had met its

burden of challenging applicants' assertion of utility, the applicants' evidence showing that several compounds exhibited antitumor activity was sufficient to convince a person skilled in the art of the utility of the compounds, and to rebut the rejection. Id. (See, also, In re Kimmel, 292 F.2d 948, 130 USPQ 215 (C.C.P.A. 1961), holding the that the utility requirement was satisfied in an application that claimed compounds and disclosed that the compounds were anti-inflammatory agents, decreased vascular permeability and were anti-bacterial agents, and the applicant provided evidence that two of the claimed compounds had the asserted activities.)

Like in Brana and Kimmel, Applicant's specification contains an assertion that CRSP-2 has utility, for example, for modulation of cellular signal transduction, regulation of gene transcription and/or regulation of cellular proliferation. (Specification at page 11, lines 23-32.) In addition, Applicant has provided Krupnick *et al.* (Reference DQ of record) and Mao *et al.* (Reference AS of record) which provide evidence that CRSP-2 inhibits cellular signal transduction and has a specific and substantial utility as disclosed in the specification. Yet, the Examiner believes that Applicant's assertion of utility is too vague or generic to satisfy 35 U.S.C. § 101, because, for example, "CRSP proteins could be involved in any of hundreds of different cellular pathways" and "no specific signal transduction pathway modulated by CRSP-2 is disclosed." (Office Action at page 3-4.)

Again, Brana and Kimmel show that the standard the Examiner is applying to this application is improper. For example, the application in Brana disclosed that the claimed compounds had "antitumor" activity against human tumor cells, but did not disclose any particular tumors that could be treated with the claimed compounds, did not disclose any particular pathway (*e.g.*, signaling pathway), protein or physiological process modulated by the claimed compounds, or disclose any explanation of how or why the compounds had antitumor activity. Thus, it appears that the Examiner would consider the disclosure of Brana's application to be too vague or generic to satisfy the utility requirement, because "antitumor" activity could apply to any of hundreds of different tumors which result from dysregulation of any of hundreds or thousands of cellular pathways or processes. This position is contrary to the Brana decision.

Like the application in Brana, this application contains a presumptively correct assertion of the utility of CRSP-2 (*e.g.*, modulation of cellular signal transduction, regulation of gene transcription and/or regulation of cellular proliferation), and Applicant has provided evidence that CRSP-2 inhibits cellular signal transduction and, thus, has a utility disclosed in the specification. (Specification at page 11, lines 23-32, Krupnick *et al.* (Reference DQ of record) and Mao *et al.* (Reference AS of record).) Accordingly, as in Brana, a person skilled in the art would be convinced that CRSP-2 has a utility asserted by Applicant in the specification. No further disclosure is required to meet the requirements of 35 U.S.C. § 101.

In view of the foregoing, the utility requirement has been met and the rejection under 35 U.S.C. § 101 and companion rejection under 35 U.S.C. § 112, first paragraph, should be withdrawn.

Rejection of Claims 61-69, 76-85, 87 and 88 Under 35 U.S.C. § 112, First Paragraph.

Claims 61-69, 76-85, 87 and 88 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

With respect to Claims 62-69, 76-85 and 87, which recite sequence identity and/or portions of SEQ ID NO:5 without reciting biological function, the Examiner states that making and using such proteins is unpredictable, that no specific biological functions of CRSP-2 are disclosed and that it is unclear how the claimed polypeptides would be used. The Examiner further states that there are no working examples showing how to make or use such polypeptides, and that the claims are broad and involve an uncharacterized protein. It is noted that the Examiner also comments on polypeptides encoded by nucleic acid sequences capable of hybridizing to sequences encoding SEQ ID NO:5, but that none of the rejected claims contain such language.

With respect to Claim 88, drawn to a pharmaceutical composition, the Examiner states that there is no disclosure of any specific disease associated with SEQ ID NO:5, there is no disclosure of how to treat a specific disease with SEQ ID NO:5, and no disclosure of doses. The

Examiner further states that there are no working examples of how to make or use such a pharmaceutical composition, and that the claim is broad and the composition involves an uncharacterized protein.

With respect to Claim 61, drawn to a method for identifying a compound that modulates the activity of a CRSP protein, the Examiner states that no specific biological functions of CRSP-2 are disclosed and that it is unclear how the effect of a test compound on the activity of CRSP-2 would be determined. The Examiner further states that there are no working examples of the claimed method, and that the claim is broad and the method involves an uncharacterized protein.

The Examiner concludes that it would require undue experimentation to make and use the inventions of Claims 61-69, 76-85, 87 and 88.

It is well established that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening." In re Wands, 858 F.2d 731, 736-37, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Id. Accordingly, enablement does not require absolute predictability, but that the person of ordinary skill in the art be able to practice the invention without undue experimentation. Id.

Claims 62-69, 76 and 77

Independent Claims 62, 66, 68, 76 and 77 have been amended to recite biological function of CRSP-2. The person skilled in the art could make and use the subject matter of these amended claims without undue experimentation. For example, the skilled person could easily produce a polypeptide consisting of an amino acid sequence that is at least 80% or 90% identical to SEQ ID NO:5, or a nucleic acid consisting of a nucleotide sequence that is at least 80% or 90% identical to SEQ ID NO:6, using a variety of methods that were conventional in the art at the time the application was filed. Producing such variant polypeptides and nucleic acids from a

parental polypeptide or nucleic acid with a known amino acid or nucleotide sequence was routine and common in the art at the time the application was filed. Once produced, the variant polypeptides or polypeptides encoded by the variant nucleic acids can be assayed for the capacity to modulate signal transduction, regulate cellular proliferation and/or regulate gene transcription using a suitable assay. Many suitable assays for assessing these activities were known in the art at the time the application was filed, and the specification provides additional guidance as to suitable assays. (Specification at page 47 *et seq.*) This routine screening is analogous to the screening of hybridomas to identify those hybridomas that produce a desired antibody which the Wands court determined was not undue experimentation. Id. Accordingly, the subject matter of Claims 62-69, 76 and 77 could be made and used by the person of skill in the art without undue experimentation and meets the enablement requirement of 35 U.S.C. § 112.

Claims 78-85

Claims 78-85 have not been amended to recite function, but the claimed subject matter is enabled because a person skilled in the art could make and use an isolated polypeptide according to any one of Claims 78-85 without undue experimentation. For example, in view of Applicant's disclosure of SEQ ID NO:5, a person skilled in the art could easily select at least 10, at least 25, at least 50 or at least 100 consecutive amino acids of SEQ ID NO:5 and produce a polypeptide that comprises the selected sequence using any suitable method. Similarly, polypeptides that contain a cystine-rich domain or region of SEQ ID NO:5 or particular regions of SEQ ID NO:5 can be easily produced based on Applicant's disclosure of SEQ ID NO:5 and the location of cystine-rich domains and regions of SEQ ID NO:5. (Specification at page 8, lines 3-28, for example.) Many methods for preparing polypeptides of a desired amino acid sequence, such as synthetic and recombinant methods, were well-known and routine in the art at the time the application was filed. The person of skill in the art could use the polypeptides, for example, to produce antibodies that bind CRSP-2 as taught in the specification. (Specification at page 31, line 31 *et seq.*) Antibodies that bind CRSP-2 are useful, *inter alia*, for detecting and/or purifying

CRSP-2 which, as taught by Applicant and demonstrated by Krupnick *et al.* (Reference DQ of record) and Mao *et al.* (Reference AS of record) modulates cellular signal transduction.

Claim 87

The subject matter of Claim 87 is enabled because the person skilled in the art could make and use the claimed fusion polypepide without undue experimentation. The recited polypeptide of any one of Claims 62, 66, 68, 72-76 and 78 is enabled for the reasons discussed above. In addition, suitable methods for producing and using fusion polypeptides or fusion proteins were well-known and conventional in the art at the time the application was filed.

Claim 88

The subject matter of Claim 88 is enabled because a person skilled in the art could make and use the claimed pharmaceutical composition without undue experimentation. Applicant provides extensive guidance in the specification. For example, Applicant provides an extensive discussion of suitable pharmaceutically acceptable carriers and discloses numerous examples. (Specification at page 43, line 8 through page 45, line 23.) Applicant also provides extensive guidance regarding dosing. For example, Applicant directs the person skilled in the art to determine dosing by *e.g.*, using standard pharmaceutical procedures to determine the ED50, LD50 and therapeutic index, and/or to determine the IC50. (Specification at page 45, line 24 through page 46, line 19.) Applicant provides further guidance for dosing based on the results obtained using such standard methods. (Specification at page 45, line 33 through page 46, line 6.) Applicant also provides guidance for determine whether it is desirable to administer the claimed pharmaceutical composition. (Specification at page 66, line 15 through page 67, line 9.) In view of the extensive guidance provided in the specification, and the level of skill in the pharmaceutical and medical arts, one skilled in the art could make and use the claimed pharmaceutical composition without undue experimentation.

Claim 61

Claim 61 has been amended to recite biological functions of CRSP-2. Many suitable assays for assessing these activities were known in the art at the time the application was filed, and the specification provides additional guidance as to suitable assays. (Specification at page 47 *et seq.*) Accordingly, the person of skill in the art could practice the invention of Claim 61 without undue experimentation, and the enablement requirement of 35 U.S.C. § 112 is satisfied.

In addition, where the scope of the claims is commensurate with the disclosure, then the statute requires only objective enablement. As stated in In re Marzocchi & Horton, 439 F.2d 220, 223, 169 USPQ 367, 369 (C.C.P.A., 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In the present case, the teachings and exemplification in the disclosure regarding how to make and use the claimed invention are commensurate in scope with the claims.

Reconsideration and withdrawal of the rejection are requested.

Objection to the Drawings

Figures 1-6 and 8 are objected to as containing numbers, letters and reverence characters that are not at least 0.32 cm in height. Replacement drawings are being filed concurrently herewith.

Information Disclosure Statement

A Supplemental Information Disclosure Statement (SIDS) was filed on June 14, 2004. Acknowledgment of consideration of the information provided therein is respectfully requested in the next Office Communication.

Applicant has not received acknowledgment of consideration of References AM-AR, BA-BT and CA-CS cited in the IDS filed on October 29, 1998 or of References AG-AR, BA-BR, CA-CT, DA-DN, EA-ES and FA-FS cited in the IDS filed on December 20, 1999. In the Office Action dated March 13, 2000 (Paper No. 12), Examiner Yucel stated that the references had not been considered because the citations did not contain dates and/or authors, and requested that Applicant indicate the relevance of the references. Examiner Yucel further stated that the references would be considered once the pertinent data were provided. (Paper 12 at pages 2-3.) In the reply to that Office Action, Applicant provided two replacement Forms PTO-1449 that contained additional bibliographic data for certain citations, and also provided remarks concerning the relevance of the cited references. (Amendment and Response filed August 17, 2000, at pages 6-9.) Acknowledgment of consideration of the references cited in the replacement Forms PTO-1449 is respectfully requested in the next Office Communication.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Robert H. Underwood

Robert H. Underwood
Registration No. 45,170
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Dated: January 26, 2005